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AUG 06 2007

REMARKS**Status of the Claims**

Claims 34-44 and 58-70 are pending herein.

Claim Rejection under 35 U.S.C. 103-Levy in view of Paliard

Claims 34-44 and 58-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,395,253 to Levy et al. (Levy) in view of US 6,562,346 to Paliard et al. (Paliard).

Applicant respectfully traverses this rejection and its supporting remarks.

The claimed invention relates to new methods for the production of microparticle compositions. As explained in the present application at paragraph [0011] onwards:

The present inventors have found that adsorption of macromolecules to microparticles can be improved by ensuring that detergent is made available for forming a complex with the macromolecules at the time of adsorption. This availability can be accomplished, for example, by separately providing a quantity of detergent at the time of macromolecule adsorption or by ensuring that the process for producing the microparticles results in a product containing a substantial amount of unbound detergent.

Thus, the application teaches two different approaches for ensuring that unbound detergent is available for forming a complex with the macromolecules at the time of adsorption.

Each of the independent claims in the present application (34, 37 and 39) requires either (I) that the microparticles are subjected to a filtration step such that about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound or (II) that the microparticles are not subjected to a washing step and the ratio of the detergent to the polymer used is such that about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound.

Among other requirements, to establish a *prima facie* case of obviousness, the prior art references must teach or suggest all the limitations of the claims. See, e.g., MPEP 706.02(j) and the cases cited therein. Levy and Paliard do meet this threshold.

With respect to limitation (II) above, the Examiner argues that while the Examples of Levy require a washing step, other portions of Levy do not. It is the Applicants position that, even assuming that portions of Levy do not require a washing step, one of ordinary skill in the art upon reviewing Levy would follow Levy's procedures, as set forth in the Examples, to

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produce microspheres. In particular, the Examples of Levy teach a method of producing microspheres comprising forming a W/O/W emulsion, evaporating the organic solvent from the W/O/W emulsion, recovering microspheres by ultracentrifugation, and washing recovered microspheres multiple times. See, e.g., the Examples of Levy. See also MPEP 2141.02.VI: A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

Moreover, it is also noted that Applicant is not simply claiming the absence of a washing step, but rather is claiming the absence of a washing step in a method where the ratio of the detergent to the polymer used is such that about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound.

Nothing anything like this is disclosed in Levy. Levy does not describe compositions with bound and unbound detergent, much less in the amounts claimed.

In this regard, the Examiner further urges that "Levy does not categorically state that the microspheres produced are free of detergents and furthermore, Levy in one of the embodiments (col. 12, lines 58-67) does not employ a washing step." The Examiner further urges that "Levy does not state that the microspheres/particles formed are free of detergent; and it flows from one of the embodiment[s] that does not use a wash step but evaporates off the organic solvent ... that the detergent is not removed and as such, the microparticles would have detergent associated." Applicant respectfully disagrees.

As an initial matter, it is noted that the solvent evaporation step referred to by the Examiner is not an *alternative* to washing, as appears to be suggested by the Examiner, but rather is a process that is used to yield solid microparticles from a dispersed oil phase (i.e., one containing polymer and solvent) in a W/O/W emulsion. (When the solvent is evaporated solid polymer particles are left behind.)

More importantly, even assuming for the sake of argument that Levy does not require a washing step, the absence of a washing step still would not necessarily produce the amounts of bound and unbound detergent claimed (i.e., about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound). In this regard, see MPEP 2112.IV:

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The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted) ...

The Examiner has not met this burden. It is noted that Applicant is not arguing that the product of Levy is completely free of detergent, rather applicant is arguing Levy does not teach or suggest a microparticle composition having bound and unbound detergent in the amounts claimed.

With respect to the Examiner's statement that the claims do not recite the amount of detergent added to make the microparticle in the emulsion, it is noted that this amount would be understood by one of ordinary skill in the art to be whatever amount is required, in the absence of a washing step or in the presence of a filtration step, to achieve a composition in which about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound.

With regard to limitation (I) above (i.e., a step in which the microparticles are subjected to a filtration step such that about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound), it is first noted that Levy does not teach a filtration step.

The Examiner had previously taken the position that "centrifugation can be considered filtration." However, in view of the materials submitted in response to the prior Office Action, the Examiner now agrees that "centrifugation is not a filtration" but urges that "filtration that collects particles or solids accomplishes [approximates?] the collection of particles or solid by centrifugation and the removal of unwanted components soluble and present in the solvent. The Hawley's Condensed Dictionary cited by application describes filtration as separation of suspended solids from liquids."

More completely, the Hawley's reference describes "filtration" as "[t]he operation of separating suspended solids from a liquid (or gas) by forcing the mixture through a porous

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barrier ...” Because filtration requires the use of a porous barrier (i.e., a filter), filtration is neither taught nor suggested by Levy. As noted above, among other requirements, to establish a *prima facie* case of obviousness, the prior art references must teach or suggest all the limitations of the claims.

Moreover, as noted above, the claimed amounts of bound and unbound detergent are neither taught nor suggested (inherently or otherwise) by Levy.

In addition to ensuring that unbound detergent is made available for complex formation with macromolecules, the processes of the present invention are advantageous relative to those of Levy, *inter alia*, because they do not require a centrifugation step. This is extremely unwieldy from a manufacturing standpoint. By avoiding the need for a centrifugation step, the manufacturing process is greatly simplified, allowing for efficient scale up and for continuous manufacturing processing, as desired.

Furthermore, in Levy, the biologically active macromolecule is incorporated into the microspheres at the time of microsphere formation. In pending claims 43, 44 and 58-61, on the other hand, the microparticle composition is incubated with a biologically active macromolecule after microparticle formation to adsorb the biologically active macromolecule to the microparticles in the composition. As noted above, by ensuring a process in which substantial detergent in the composition remains unbound to the microparticles, detergent is made available for forming a complex with the macromolecules at the time of adsorption. See, e.g., paragraph [0011] of the present specification.

With respect to the cross-flow filtration as claimed in claim 36, the Examiner argues that because water is used to remove detergent in the cross-flow filtration process, this appears to be “equivalent to” washing, so the cross-flow filtration step of claim 34 “reads on” the wash step of Levy. However, the washing steps of Levy (which are performed in conjunction with centrifugation) have nothing to do with filtration, which as noted above involves the use of porous media to separate suspended solids from a liquid. As noted above, to establish a *prima facie* case of obviousness, the prior art references must teach or suggest all the claim limitations, including the general limitation of filtration and the more specific limitation of cross-flow filtration in claim 36.

With respect to SDS, the Examiner continues to refer to the disclosure of 0.1% SDS in Section 5.3.2. It thus appears that the Examiner continues to fail to recognize that Levy’s use of

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SDS occurred after formation of DNA containing microspheres and that SDS was used to disrupt the microspheres in order to release entrapped DNA from the microspheres (see col. 19, ll. 8-13). In particular, at column 19, lines 8-10, Levy specifically teaches incubating DNA-containing microspheres in excess TE buffer with and without 0.1% SDS. At column 19, lines 11-13, Levy discloses that SDS was used to establish that charge-related associations between poly-L-lysine and DNA contribute to the DNA release and/or extraction mechanism. Thus, in Section 5.3.2, the SDS was used as an *analytical reagent* to release condensed DNA from the microspheres.

In contrast, in Applicants' claimed invention, detergent is used in a microparticle formation step. More specifically, detergent is included in step (a) of the independent claims, in forming an emulsion.

Paliard, which cited for its disclosure of CTAB as a detergent as claimed in claims 38 and 40, does not make up for the above noted deficiencies in Levy. For example, as elsewhere in the art at the time of the invention, washing is taught in Paliard in Example 5 (see col. 23, lines 53-55).

"The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness." MPEP 2145.X.D.3. Citing *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).

Furthermore, because the SDS was used as an analytical reagent in Levy as noted above, the Examiner's assertion that it would have been obvious to use the CTAB of Paliard in place of the SDS of Levy is not persuasive.

For at least the above reasons, it is respectfully submitted that the cited references do not support a *prima facie* case of obviousness against claims 34-44 and 58-67.

Reconsideration and withdrawal of the rejection of the claims under U.S.C. 103(a) as unpatentable over O'Hagan in view of Paliard are respectfully requested.

Claim Rejection under 35 U.S.C. 103-O'Hagan

Claims 34, 35, 36, 42 and 43 are rejected under 35 U.S.C. 103(a) as unpatentable over US 6,086,901 to O'Hagan et al. (O'Hagan). Applicant respectfully traverses this rejection and its supporting remarks.

As noted above, each of the independent claims in the present application, including claim 34, requires either (I) that the microparticles are subjected to a filtration step such that

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about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound or (II) that the microparticles are not subjected to a washing step and the ratio of the detergent to the polymer used is such that about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound.

With respect to limitation (II), O'Hagan describes washing and centrifugation. See, for instance, Example 1, col. 14, lines 62-63 (washed three times using centrifugation) and Example 3, col. 16, lines 3-4 (also washed three times using centrifugation). This is noted by the Examiner. However, the Examiner further urges that "there is no demonstration in applicant's specification that not subjecting the microparticles to a washing step provides unusual/unexpected results to the microparticles." Unexpected results, of course, can be used to overcome a *prima facie* case of obviousness. See, e.g., MPEP 716.02(a)-(g). Here, however, a *prima facie* case has not been made out.

In particular, to establish a *prima facie* case of obviousness, the prior art reference must teach or suggest all the claim limitations, among other requirements. O'Hagan does not teach or suggest a process in which microparticles are not subjected to a washing step. To the extent that the Examiner may not be giving proper weight the negative aspect of the claim limitation, see, e.g., MPEP 2173.05(i). ("The current view of the courts is that there is nothing inherently ambiguous or uncertain about a negative limitation.")

Moreover, as noted in paragraph [0011] of the specification, techniques in which microparticles are washed multiple times with water, such as the process of O'Hagan, remove essentially all unbound detergent, resulting in a final product in which greater than 99% of the remaining detergent is bound to the particles. Thus O'Hagan further does not teach or suggest a process by which a microparticle composition is produced in which about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound.

With respect to limitation (I), O'Hagan does not teach or suggest a filtration step, much less one that would provide bound and unbound detergent in the amounts claimed.

This is even more clearly apparent with respect to the cross-flow filtration step claimed in claim 36. In this regard, the Examiner argues that the process of claim 36 "reads on washing because in the cross-flow filtration process, 4 liters of deionized water (Example 5) are used and

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the removal of the water appears to approximate the process of filtration/washing." As with Levy, however, the washing steps of O'Hagan (which are performed in conjunction with centrifugation) have nothing to do with filtration, which as noted above involves the use of porous media to separate suspended solids from a liquid. Claim 36 is even more remote from O'Hagan, because it involves a particular type of filtration.

The Examiner correctly notes that claim 42 is a product by process claim. Nonetheless, claim 42 is neither taught nor suggested by O'Hagan. For example, the product limitation of a microparticle composition in which about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound is neither taught nor suggested by O'Hagan. As noted above, techniques in which microparticles are washed multiple times with water, such as the process of O'Hagan, remove essentially all unbound detergent, resulting in a final product in which greater than 99% of the remaining detergent is bound to the particles.

For at least these reasons, it is believed that claim 34, as well as claims 35, 36, 42 and 43 depending therefrom, are patentable over O'Hagan. Reconsideration and withdrawal of the rejection of these claims over O'Hagan are respectfully requested.

CONCLUSION

Applicants submit that the claims of the present invention are in condition for allowance, early notification of which is earnestly solicited. Should the Examiner be of the view that an interview would expedite consideration of this Amendment or of the application at large, request is made that the Examiner telephone the Applicant's attorney at (703) 433-0510 to resolve any outstanding issues.

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